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DRESS syndrome: A literature review and treatment algorithm

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms, known by its acronym in English as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), clinically manifests with fever, facial edema, lymphadenopathy, a morbilliform rash, and organ involvement. Laboratory results reveal leukocytosis, atypical lymphocytes, eosinophilia, and alterations of liver and kidney function tests. The actual incidence of DRESS is unknown, because it may vary depending on the type of medication and the immune status of each patient; also, because many cases remain undiagnosed or untreated. The drugs most associated with DRESS include antiepileptics, antibiotics, antituberculosis, and non-steroidal anti-inflammatory agents (NSAIDs). Its diagnosis is sometimes made late and can become a challenge. The diagnostic criteria proposed by the international Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) help to establish the diagnosis through a score system based on clinical and laboratory findings. The first step to identify the culprit is a thorough clinical history that includes all suspects, emphasizing those most known to cause DRESS syndrome according to the context and the literature. A skin biopsy may also be helpful in the diagnostic process. Patch testing is the test of choice to search for the culprit in cases of DRESS. Regarding prognosis, the estimated mortality due to DRESS is 3.8%. The main causes of mortality include fulminant hepatitis and liver necrosis. Several indicators of poor prognosis have been identified and these include an eosinophil count above 6000 $\times$ $10^3/\mu L$, thrombocytopenia, pancytopenia, leukocytosis and coagulopathy. This article aims to review the evidence available regarding the epidemiology, pathophysiology, clinical and laboratory findings, diagnosis, and treatment of DRESS.

Keywords: Drug hypersensitivity, Drug reaction, DRESS, DIHS, Eosinophilia

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms, known by its acronym in English as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), is a serious adverse reaction induced by drugs with a late clinical presentation,[1] which usually begins with prodromal symptoms consisting of general malaise, pruritus, and fever (between 38 and 40 °C). Subsequently, it progresses to skin and systemic involvement with a morbilliform rash, diffuse scaling, facial edema, and erythroderma as well as lymphadenopathy, hematological

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abnormalities, and end organ damage (liver, kidney, heart, lungs, endocrine system, etc.).[2]

The graphene "R" of the acronym DRESS is used to refer to the term "reaction" instead of "rash", because some cases of DRESS can manifest with visceral involvement in absence of cutaneous symptoms.[3] On the other hand, the nomenclature of DRESS syndrome can cause confusion because eosinophilia is not an indispensable criterion for its diagnosis and therefore, some groups have used the term drug-induced hypersensitivity syndrome or DIHS for its acronym in English. (Drug Induced Hypersensitivity Syndrome). In this review we will refer to the term DRESS as described by Bocquet.[1,3]

EPIDEMIOLOGY

The actual incidence of DRESS is diverse, because it may vary depending on the type of medication and the immune status of each patient; also because many cases remain undiagnosed or untreated. In the general population, the estimated incidence is more than 1 case per 10 000 exposures to medications.[4] Other data show an incidence of 0.9/100 000 inhabitants and 10 cases per million in the general population.[5,6] In hospitalized patients, the incidence ranges from 2.18 to 40/100 000 inpatients.[7–9] A higher incidence of DRESS has been observed in the black population and in women.[7,10,11] Despite the treatment instituted, the mortality rate in DRESS can range from 3.8% to 10%.[7,12] In one prospective multinational study, the mortality rate was 1.7%.[13]

ETIOLOGY

At least 44 medications have been associated with DRESS. Those most frequently implicated are aromatic anticonvulsants (phenytoin, carbamazepine, and phenobarbital); sulfonamides; sulfones (dapsone); nonsteroidal anti-inflammatory drugs (piroxicam, ibuprofen, and diclofenac); beta-lactam antibiotics, vancomycin, allopurinol; minocycline and antiretrovirals.[11,12,14–18] However, in 10–20% of cases, the causative drug cannot be identified.[13] Antibiotics such as amoxicillin can cause DRESS, however, in most cases, this drug acts as an aggravating factor in DRESS induced by other drugs.[19] (Table 1)

PATHOPHYSIOLOGY

Although the exact mechanism of DRESS has not been determined, 3 key components have been considered within its pathophysiology; the first is a genetic susceptibility in relation to certain alleles of the human leukocyte antigen (HLA);[10,20] the second factor is related to an alteration in the metabolic pathways of drugs, mainly aromatic anticonvulsants;[21,22] and finally a reactivation of HHV 6,[23,24] which leads to an inflammatory response mediated by T lymphocytes resulting in tissue damage.

Pharmacogenetic studies have found an association between HLA haplotypes and DRESS susceptibility. HLA-B * 5701 has been associated with an increased risk of developing abacavir-induced DRESS.[25] The presence of HLA-B * 5801 in the Han ethnic group of China is a risk factor for Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and DRESS caused by allopurinol;[26] HLA-DR3, HLA-DQ2 and HLA-A * 31: 01 have been associated with DRESS induced by carbamazepine.[27] These allelic markers have a

Group	Drugs
Antiepileptics	Aromatic antiepileptic drugs (Carbamazepine, lamotrigine phenobarbital, phenytoine, oxcarbazepine)
Antibiotics	Amoxicillin, ampicillin, azithromycin, levofloxacin, minocycline, sulfamethoxazole-trimethoprim, vancomycin
Antituberculosis agents	Ethambutol, isoniazid, pyrazinamide, rifampin
NSAIDS	Aspirin, celecoxib, diclofenac, ibuprofen, piroxicam
Others	Allopurinol, amitriptyline, dapsone, hydroxychloroquine, imatinib, nevirapine, omeprazole, sulfasalazine

Table 1. Most commonly associated drugs. *Adapted from Cho Y T*[73].

high negative predictive value, suggesting that they are necessary but not sufficient to produce an allergic response.[28,29]

Aromatic anticonvulsants such as phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and lamotrigine, are metabolized by hepatic cytochrome P450 (CYP) enzymes;[30] therefore, a defect in the detoxification function mediated by epoxide hydroxylase or glutathione transferase can lead to the production of reactive oxygen metabolites, these accumulate and cause cellular toxicity, generating alarm signals that can stimulate T lymphocytes and induce an immune response.[22,31]

HHV-6 typically resides latently in T lymphocytes and monocytes and can be reactivated during immunosuppression. The primary infection is acquired through droplets at around 6–15 months of life. It is usually asymptomatic but in 20% of cases it can manifest with fever, gastrointestinal and respiratory symptoms, as well as neurological symptoms such as seizures. A viral reactivation of HHV-6 during the course of DRESS, [as well as Epstein-Barr virus (EBV), cytomegalovirus (CMV) and HHV-7] has been demonstrated through increased immunoglobulin G (IgG) against HHV-6 and the identification of viral genetic material.[32]

Regarding viral reactivation, it has been proposed that an immune response directed against the drug leads to a viral reactivation, and this would explain most of the clinical manifestations of DRESS.[33] The long latency period between drug administration and the onset of DRESS syndrome manifestations would be the consequence of the period necessary to reactivate and amplify viral replication. It is possible that some of the drugs involved act directly in the transcription of viral DNA, as with valproic acid, which inhibits histone deacetylases, favoring the reactivation of latent viruses.[33] Most drugs associated with DRESS have immunomodulatory properties and their prolonged administration could have an immunosuppressive action favoring viral reactivation. In the specific case of anticonvulsants, these can lead to transient hypogammaglobulinemia.[34,35]

Activated T lymphocytes produce large amounts of pro-inflammatory cytokines such as: tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and interferon gamma (IFNγ), which are responsible for the state of generalized inflammation and organ failure associated with DRESS. Additionally, these cytokines promote the expansion of populations of regulatory T lymphocytes (Tregs) in the acute phase (0–11 days) of the disease, which are susceptible to infection by HHV-6; this expansion leads to an altered Treg function that ultimately contributes to the immune response observed in DRESS after viral reactivation. This response seen in DRESS is not observed in other severe skin diseases such as SJS/NET, which can be an important differentiator between one and the other. Furthermore, it seems that in the subacute stage of the disease (11–36 days) the Treg cells induced by IL-6 can contribute to the change from a Treg to a Th17 response, which induces a response mediated by these cells that promotes inflammation.[36–38]

CLINICAL MANIFESTATIONS

In general, DRESS Syndrome usually begins with prodromal symptoms such as general malaise, pruritus and fever (between 38 and 40 °C), the latter is generally preceded by skin manifestations for several days and may persist for weeks. Lymphadenopathies are present in up to 75% of patients. These are typically soft in consistency, measure between 1 and 2 cm and are in the cervical, axillary, and inguinal regions and may present with any of 2 histopathological characteristics: a benign pattern and pseudolymphoma-like features.[2]

In most patients the reaction occurs 2 to 6 weeks after starting the drug, this latency period is longer than in most drug eruptions. However, in patients re-exposed to the causative drug, as well as in those with hematological and liver function alterations, the symptoms may appear quicker and with greater severity.[4,36]

Skin involvement usually begins as a pruriginous morbilliform rash, which rapidly progresses, becoming diffuse and infiltrating. Initially it may involve the face, the upper part of the trunk, the upper extremities, and finally the lower extremities. A rash suggestive of DRESS is considered when more than 50% of the total body surface area is involved. Additionally, vesicles or bullae (probably related to the edema of the dermis), atypical target

lesions, purpuric lesions and small sterile follicular pustules may appear. About half of the patients present facial edema, which is symmetrical, persistent, and located in the midface and periorbital region, which can be confused with angioedema. Mucous membrane involvement occurs in up to 50% of patients. It usually involves a single site (cheilitis, erythematous pharynx, hypertrophic tonsils), and can sometimes progress to erosions.[39,40] Over time the skin rash takes on a more purplish appearance associated with diffuse scaling, and in 20–30% of cases the erythema progresses to erythroderma (diffuse erythema and scaling affecting more than 90% of the total body surface area). These clinical manifestations can persist for weeks to months after discontinuing the offending drug.[16]

The hematological manifestations in DRESS include leukocytosis (preceded by leukopenia and lymphopenia), the presence of atypical (reactive) lymphocytes, thrombocytopenia, and anemia. Eosinophilia occurs in 60–70% of cases and can often take 1–2 weeks to appear and can even occur after liver enzymes have returned to normal. Hemophagocytic syndrome (fever, jaundice, hepatosplenomegaly, low ferritin, elevated lactate dehydrogenase (LDH), and increased triglycerides) can also occur rarely. Up to 90% of patients have affectation of at least 1 organ, the liver being the most commonly affected one (60–80% of cases); it generally manifests as asymptomatic hepatitis, but hepatomegaly and jaundice may also be present.[3,36,39]

Liver function tests may be abnormal and include an increase of more than 2 times the normal value of the enzyme alanine aminotransferase (ALT) and a value greater than 1.5 of the alkaline phosphatase (FA). These changes are generally mild and transient; however, the elevation of liver enzymes can persist for several days after stopping the drug and can even take months to resolve. The main cause of mortality in DRESS is due to hepatic necrosis, which can be extensive and cause severe liver failure with coagulopathy, encephalopathy, and ALT greater than 10 times the upper limit.[41,42]

Renal alterations may occur in up to 30% of cases, these may include a moderate increase in creatinine and BUN (blood urea nitrogen), proteinuria, and alterations in the urinary sediment with the presence of eosinophils. In most cases, the kidney disorder is mild and resolves after stopping the causative drug; however, there may be cases where severe interstitial nephritis occurs and progresses to kidney failure. The drugs most commonly known to cause kidney injury are: allopurinol, carbamazepine, and dapsone. Patients with underlying kidney disease and the elderly are at higher risk of presenting kidney failure.[2,13]

Pulmonary disease occurs in up to 25% of DRESS cases, it can present with dyspnea, nonproductive cough, hypoxemia, and signs of interstitial pneumonitis and/or pleural effusion on chest x-ray and CT-scans. The drug most commonly associated with lung damage is minocycline.[42]

Cardiac involvement, such as eosinophilic myocarditis or pericarditis, can occur months after stopping the drug and be potentially fatal. Its typical signs and symptoms include chest pain, tachycardia, dyspnea, and hypotension. There may be a rise in cardiac enzymes, cardiomegaly on chest X-ray, and ST and T-wave changes, sinus tachycardia, and arrhythmias on the EKG. Heart involvement has been associated more frequently with minocycline and ampicillin.[2]

The gastrointestinal tract can also be affected and manifests with dehydration and gastrointestinal bleeding, which requires an upper gastrointestinal endoscopy (EGD) and colonoscopy for its evaluation.[2]

Endocrine abnormalities present as a long-term sequela, 2 to 4 months after stopping the drug, and the most common finding is thyroiditis. Clinical manifestations of thyroiditis include palpitations, irritability, sleep disturbances, among others. Routine thyroid function tests are recommended for at least 2 years after the event. Other manifestations such as pancreatitis and type 1 diabetes mellitus (DM) can appear between 3 weeks and 10 months after the start of DRESS.[2,3,36]

Neurological manifestations are infrequent and include meningitis and encephalitis. These may manifest 2 to 4 weeks after the start of DRESS and may be related to the reactivation of HHV-6. Headache, seizures, cranial nerve palsy, and muscle weakness are some of the symptoms that may be present.[43]

ATYPICAL MANIFESTATIONS

There are other less frequent manifestations such as scarring conjunctivitis, related to lamotrigine and levetiracetam, oral ulcers related to celecoxib and ethambutol, dysphagia related to amoxicillin, and even more unusual, inverse typhus fever, related to paracetamol, phenytoin, and metamizole.[44]

Other organ systems that can be affected are the musculoskeletal system with myositis and increased creatine phosphokinase (CPK), and the peripheral nervous system with polyneuritis and uveitis, among others.[3]

DIAGNOSIS

The diagnosis of DRESS is sometimes made late and can be challenging, due to its variety of clinical presentations. The original diagnostic criteria were proposed by Bocquet et al[1] and included a rash due to drugs, hematological alterations (eosinophils greater than 1500 $\times$ 10^9/L and the presence of atypical lymphocytes) and systemic manifestations (lymphadenopathy, liver, kidney, lung, and cardiac involvement). These were replaced by the criteria proposed by the RegiSCAR group. These criteria are based on clinical and laboratory findings; by means of a scoring system, they allow the establishment of the diagnosis as "a negative case", "a possible case", "a probable case", and "a

Criteria	SCORE			
	−1	0	+1	+2
Fever greater than or equal to 38.5 °C	No	Yes		
Lymph node enlargement		No/U	Yes	
Eosinophils			700–1499/μL	≥1500/μL
Eosinophils, if leukocytes are <4,000			10–19.9%	≥20%
Atypical (or reactive) lymphocytes		No/U	Yes	
Extensive rash (>50% TBSA)		No/U	Yes	
Rash suggestive of DRESS	No	U	Yes	
Biopsy suggestive of DRESS	No	Yes/U		
Hepatic impairment		No/U	Yes	
Renal impairment		No/U	Yes	
Lung manifestations		No/U	Yes	
Muscle/Heart manifestations		No/U	Yes	
Pancreatic impairment		No/U	Yes	
Impairment of other organs		No/U	Yes	
Resolution in ≥15 days	No/U	Yes		
Evaluation of other potential causes: ✔ ANAS ✔ Blood cultures ✔ Serology for Hepatitis A/B/C ✔ Chlamydia/Mycoplasma pneumoniae ✔ Other serologies/PCR/cultures If none is (+) and ≥3 of those mentioned are (−)			Yes	

Table 2. RegiSCAR scoring system.[22] **U: unknown.Final score <2 (negative case); 2 to 3 (possible case); 4 to 5 (probable case) and> 5 (definitive case).*

definitive case" of DRESS.[45] These diagnostic criteria are presented in Table 2.

It is important to differentiate DRESS from other diseases that involve the skin, such as viral infections and vasculitis; which may be accompanied by peripheral eosinophilia; as well as other conditions like systemic lupus erythematosus, Kawasaki disease, and scalded skin syndrome. Similarly, erythroderma can be secondary to the exacerbation of a pre-existing skin disorder, such as psoriasis or atopic dermatitis.[46,47]

DRESS can also be confused with other severe drug-related skin reactions such as SJS and TEN, which are clinically characterized by a shorter latency period (5–28 days) and the presence of necrotic keratinocytes and necrosis of the epidermis.[48] On the other hand, in generalized acute pustulosis (AGEP), the latency period is approximately 48 h, and it is characterized by the presence of non-follicular sterile pustules. It resolves usually spontaneously in a few days, and after suspending the drug involved.

HISTOLOGICAL FINDINGS

The presence of the following findings in skin biopsies can guide the diagnosis of DRESS: spongiosis, acanthosis, vacuolization, lymphocytic infiltrate in the papillary dermis, and perivascular predominance, variable presence of eosinophils, atypical lymphocytes, or even granulomas.[49]

CULPRIT DRUG IDENTIFICATION

Patch testing

Traditionally, this is the test of choice to search for the culprit in cases of DRESS if LTT is not available.[50] Its performance depends mainly on the drug used and it has been shown to be safe in immunocompetent patients.[51]

The first step to identify the culprit is a thorough clinical history that includes all suspects, emphasizing those most known to cause DRESS syndrome according to the context and the literature.

Antibiotics such as beta-lactams, vancomycin, and quinolones, as well as other drugs such as carbamazepine and proton pump inhibitors are more likely to produce a truly positive patch test result, whereas other drugs such as allopurinol and sulfasalazine have shown to produce false negative results. Therefore, the performance of the drugs being tested should be known in advance and taken into consideration when it comes to interpreting the results.[51]

All tests should be performed 4–6 weeks after the reaction, and the patient should not be receiving immunosuppressive therapy or systemic corticosteroids for at least 4 weeks; this is in order to reduce the rate of false negative results. The most used and most recommended concentration is 10% in petroleum jelly using commercial forms of the drug but it may go up to 30%. The concentration must be determined considering the recommendations for each drug in particular.[52] It is recommended to make an initial reading 48 h after placing the patch and a second reading in 96 h. However, with some medications, late readings (7–10 days) may be recommended.[53]

Intradermal test

Intradermal tests have been shown to be useful in searching for the culprit in DRESS. An intradermal test is recommended when the patch result is negative if the implicated drug is available intravenously. The readings should be after 6 and 24 h.[50,51]

For some medications, such as beta-lactams, intradermal tests may perform better than patches.[51]

Lymphocyte transformation test

This is a test that may be useful in identifying the culprit drug by measuring lymphocyte proliferation in response to the drug in question. It should be done within 4–8 weeks of the reaction and preferably in the first 6 months. It has a sensitivity of up to 73% and a specificity of 85%, which combined with the patch test can increase the probability of diagnosis.[54–56]

One of its main advantages compared to skin tests is that, as it is an *in vitro* method, there is no possibility of reproducing the reaction after drug exposure, and even though the chance for this is slim, it may be relevant in immunosuppressed patients.

There are other tests, such as cytokine release assays by ELISA, for example, for the detection of

IFN-γ in DRESS. However, there is insufficient evidence to recommend these methods routinely.[50]

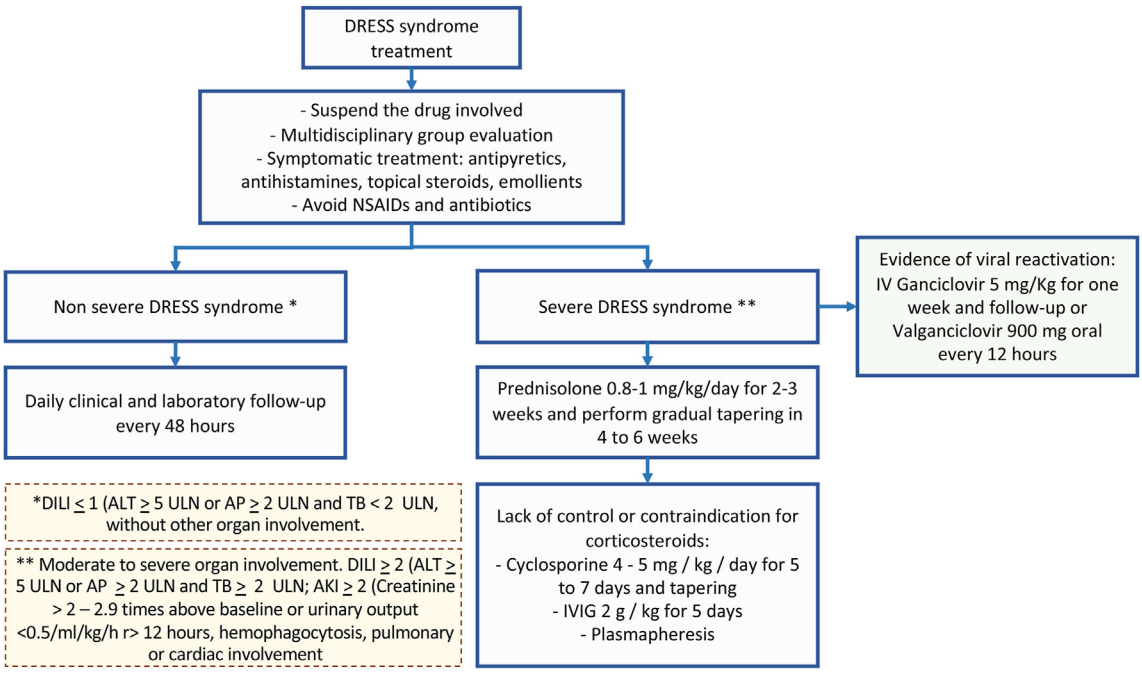
Treatment

The French group headed by Descamps et al[57] proposes a treatment algorithm, which is summarized in 4 scenarios. The first scenario occurs in the absence of signs of severity and requires treatment with topical corticosteroids, interruption of the suspected drug, emollients, and antihistamines. The presence of any sign of severity such as transaminases 5 times higher than the normal value, kidney failure, lung disease, hemophagocytosis, or cardiac abnormalities define the second scenario, and its management should include systemic steroids such as prednisolone (1 mg/kg per day). The third scenario occurs in the presence of any life-threatening sign (hemophagocytosis, spinal cord failure, encephalitis, liver failure, respiratory failure), and it should be treated with corticosteroid as well as intravenous immunoglobulin (IVIG) at a dose of 2 g/kg for five days. Finally, a fourth scenario is given by the presence of signs of severity together with the confirmation of viral reactivation and it should be treated with corticosteroids, IVIG and antivirals such as ganciclovir.

The document by Cabanas et al provides an expert consensus-based stepwise guideline for the treatment of DRESS syndrome, including evidence-based analysis of literature, which can aid the decision making process regarding treatment. Fig. 1 depicts a treatment algorithm, modified from the Spanish group's guidelines.[50]

The Japanese group, led by Shiohara T et al, in its 2019 guideline proposes a scoring system using clinical and laboratory variables. This system can be used to establish severity, predict prognosis, and stratify the risk of developing serious complications, such as fatal CMV disease. It also makes suggestions regarding treatment that could be useful to optimize therapeutic efficacy and prevent relapses related to treatment.[38]

The use of systemic corticosteroids for the treatment of DRESS has not been studied in randomized trials, however, it is currently the most accepted treatment. Its early administration is recommended for almost all cases of DRESS and the dose should



NSAIDs: non-steroidal anti-inflammatory drugs; IVIG: intravenus immunoglobulin; AP: alkaline phosphatase; ULN: upper limit of normality; TB: total bilirubin; ALT: alanine aminotransferase; AKI =: acute kidney injury; IV: intravenous

Fig. 1 Depicts the recommended treatment algorithm for DRESS syndrome. Initially there are some general recommendations for any DRESS syndrome case. The algorithm further discriminates the treatment based on the severity of each case depending on whether it is a non-sever or a severe case. This algorithm was modified from Cabañas R et al.[50]

start at a minimum of 1 mg/kg/day of prednisolone. Gradual tapering should be done in 3 to 6 months to avoid relapses.[51] Sometimes it may be necessary to apply intravenous pulses of methylprednisolone at a dose of 30 mg/kg for 3 days. Its use is recommended not only for the control of clinical symptoms during the acute phase, but also to prevent the development of autoimmunity that can occur later on.[58,59] Chiou and colleagues[58] observed in 30 cases of DRESS, that patients treated with systemic corticosteroids had significant improvement in both clinical manifestations as well as laboratory results, without presenting secondary skin and soft tissue infections.

There are reports of patients who have been treated with high doses of IVIG successfully. Although its mechanism of action is not known, IVIG antibodies appear to neutralize the virus.[60] Possible adverse effects include infusion reactions during administration, thromboembolic events, anaphylaxis, acute renal failure, hemolytic anemia, aseptic meningitis, and pulmonary edema. In a prospective multicenter study, carried out in France, Joly et al[61] observed that of the 6 patients with DRESS treated IVIG, 5 experienced serious adverse events and 4 had to be treated with oral corticosteroids, due not only to adverse effects but also to the absence of clinical response; concluding that IVIG should not be used as monotherapy in DRESS.

In case reports, the use of cyclosporine appears to be an alternative to corticosteroids, with much shorter treatment times and with an adequate safety profile.[62] To date, 5 cases of DRESS treated with cyclosporine have been reported in the literature.[63–67] Other medications that have been used are cyclophosphamide, interferon, mycophenolate mofetil, and rituximab.

N-acetylcysteine is a glutathione precursor that modulates the production of pro-inflammatory cytokines and the expression of adhesion molecules. It is involved in the detoxification pathway of anticonvulsants and, therefore, its use is recommended for the treatment of DRESS induced by these drugs.[68] An adverse effect related to its application is angioedema, which seems to resolve rapidly once the drug is discontinued.[69]

Fig. 1 shows our proposed treatment algorithm, which includes some general measures that apply to all cases of DRESS syndrome as well as specific actions to take depending on the severity of each case.

Autoimmunity

Patients with DRESS are at risk of developing systemic autoimmune sequelae, which can appear anywhere from months up until 4 years after the resolution of the cutaneous manifestations and acute systemic involvement. The autoimmune manifestations may be a continuation of the organ involvement that appeared during the acute phase.[70] This is thought to occur due to a gradual loss of regulatory T lymphocyte function and consequently a loss of tolerance to autoantigens; the latter, explained by the fact that drugs non-covalently bound to the cleft of the major histocompatibility complex (MHC), can alter the peptide repertoire. Systemic corticosteroids administered during the acute phase of the disease appear to have a preventive role in these conditions, by restoring the activity of regulatory T lymphocytes.[46,71]

The Taiwanese team, Chen YC et al published the long-term sequelae observed in DRESS patients and identified a rate of 11.5% of sequelae among 52 patients. The most common sequelae included autoimmune thyroiditis. Other autoimmune sequelae identified in this study included diabetes mellitus, autoimmune hemolytic anemia, and alopecia.[72]

Other autoimmune sequelae that have been reported include autoimmune blistering disorders, sclerodermoid cutaneous changes, systemic lupus erythematosus, and enteropathy.[70]

Follow-up

The skin rash and organ damage gradually resolve after stopping the involved drug. On average the recovery period is 6 to 9 weeks; however, in more than 20% of cases the disease can persist for several months with relapses. There are several factors described in relation to a longer course, such as severe liver involvement and the presence of atypical lymphocytes.[2]

The estimated mortality from DRESS is 3.8%, mainly due to fulminant hepatitis and liver necrosis. Among the indicators of negative prognosis

are eosinophil counts above 6000 $\times$ 10^3/μL, the presence of thrombocytopenia, pancytopenia, leukocytosis, coagulopathy, the presence of comorbidities such as chronic kidney disease, and the use of medications such as minocycline and allopurinol.[2]

Patients with DRESS are at risk for long term sequelae and therefore long-term monitoring focused on detecting autoimmune disease is recommended for them.

CONCLUSIONS

DRESS-type delayed hypersensitivity reactions are an important clinical condition associated with different medications. These reactions often develop in individuals with a genetic predisposition. Given the potentially severe outcomes seen in DRESS, the recognition of the clinical manifestations of these reactions allows the timely diagnosis and treatment of the patients and helps to avoid specific organ damage. It is essential that the allergist is familiar with the treatment options proposed by the different working groups worldwide (French, Spanish, and Japanese groups) so that each patient's risk is stratified, and adequate treatment is offered.

Finally, identifying the culprit is one of the fundamental roles for the allergology group, since this will determine the diagnostic tests in the future as well as the avoidance measures. As part of the treatment process, the outpatient follow-up allows the identification of sequelae after the event and the treating physician must be aware of the monitoring process that must be undertaken with these patients.

Abbreviations

DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms; DIHS, Drug Induced Hypersensitivity Syndrome; HLA, Human Leukocyte Antigen; SJS, Stevens Johnson Syndrome; TEN, Toxic Epidermal Necrolysis; Tregs, regulatory T lymphocytes; NSAID, Non-steroidal anti-inflammatory drugs; IVIG, Intravenous immunoglobulin; AP, Alkaline phosphatase; ULN, Upper limit of normality; TB, Total bilirubin; ALT, Alanine aminotransferase; AKI, Acute kidney injury; IV, intravenous.

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Author contributions

All authors declare that they have made substantial contributions to the conception and design, literature review and interpretation of the manuscript and given final approval of the version to be published.

Ethics statement

Ethics approval does not apply to this work given that this is a literature review, and no patient information is disclosed.

Authors' consent

All authors give their consent to the publication of this manuscript.

Declaration of competing interest

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